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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,803	11/07/2001	Fernand Labrie	P/1259-637	3989

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,803	LABRIE, FERNAND	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *6-11,21,24 and 28-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 12-20, 22-23, 25-27, and 34-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on February 17, 2004 wherein claims 12-13 and 34-35 have been amended.

Currently, claims 1-43 are pending in this application.

It is noted that claims 6-11, 21, 24, and 28-33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, of record in the previous Office Action dated August 13, 2003.

As indicated in the previous Office Action, the claims have been examined insofar as they read on the elected specie which are the species of EM-652.HCl in claims 19 and 41 for the SERM compound, 17β-estradiol in claim 20 for as an estrogen, and dehydroepiandrosterone (DHEA) for additional agent in claim 2, and thus claims 1-5, 12-20, 22-23, 25-27, and 34-43 read on the elected species and examined on the merits herein.

Applicant's amendment filed February 17, 2004 with respect to the rejection of 12-18 and 34-40 made under 35 U.S.C. 112 second paragraph for use of the indefinite expression " R100 is a bivalent moiety....B-ring by.. " of record stated in the Office Action dated August 13, 2003 have been fully considered and found persuasive to overcome the rejection only as to " R100 is a bivalent moiety....B-ring by.. ".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 22-23, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular selective estrogen receptor modulator (SERM) compounds having the formula in claims 12-16 herein and the particular estrogens in claim 20, further in combination with the particular additional agents herein in the claimed composition, does not reasonably provide enablement for any selective estrogen receptor modulator and any estrogens, recited in the claims herein, for the same reasons of record in the Office Action dated August 13, 2003.

The recitations, "one selective estrogen receptor modulator" and "one estrogen", are seen to be merely functional language.

Even regarding the recitation for compounds in claims 3-5 and 25-27, one skilled in the art would clearly recognize that the recitation would encompass numerous compounds containing various structurally different substituents.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a pharmaceutical composition for therapeutic treatments.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since the broadest claims (i.e., claims 1-2) reads on any "selective estrogen receptor modulator" and "estrogen" employed in the composition herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A

definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "one selective estrogen receptor modulator" and "one estrogen" recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for each kind of functional compounds for the composition in claims.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).
The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as

discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) the ***combination*** of any compounds represented by "one selective estrogen receptor modulator" and "one estrogen", which may encompass more than a thousand compounds. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the

pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

As discussed above, only those particular compound for each kind of functional compounds employed in the composition herein is disclosed in the specification. Moreover, it is noted that the specification merely provides the testing of two particular SERMs (i.e., EM-652 and EM-800) in working examples of the instant specification. Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the compounds in the claimed composition. See MPEP § 716.02(d).

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice

the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

Response to Argument

Applicant's arguments filed February 17, 2004 with respect to this rejection made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement have been fully considered but are not deemed persuasive as further discussed below.

Applicant arguments that "It is permissible for a patent claim to recite a class of materials when, as here, there is reason to expect each member of the class to perform similarly in the context of the invention. In the present claims, there are recitations of a classes of like-functioning materials (e.g., estrogens) such recitations of a class of materials is proper under 35 U.S.C. 112, first paragraph, wherever the specification would lead one of skill in the art to expect and predict that specific members of the class will interchangeably provide the same function in the invention", have been considered but not found convincing.

As noted in MPEP 2111, during patent examination, claims are given their **broadest** reasonable interpretation. It is proper to use the specification to interpret what the applicant meant by a word or phrase recited in the claim, However, it is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994) for example. In this case, as discussed in the previous Office Action,

the instant claims read on the combination of any compounds represented by "one selective estrogen receptor modulator" and "one estrogen", which broadly encompass those known and unknown two classes functional compounds of selective estrogen receptor modulators and estrogens as of the instant filing date, especially those future known selective estrogen receptor modulators and estrogens, requiring additional or future research to establish or verify their usefulness as selective estrogen receptor modulators and estrogens.

Therefore, discussed above, to practice the claimed invention herein, a person of skill in the art would have to exercise *undue experimentation* to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 12-20, 22-23, 25-27, and 34-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the same reasons of record in the Office Action dated August 13, 2003.

The recitations, "derivative" and "derivatives" in claims 1-2 and 22-23 render claims 1-5, 12-20, 22-23, 25-27, and 34-43 indefinite. The recitations, "derivative" and "derivatives" are not defined in the specification. Hence, one of ordinary skill in the art

could not interpret the metes and bounds as to "derivative" and "derivatives", in the claim. Therefore, the scope of claim is indefinite as to the composition encompassed thereby.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 12-20, 22-23, 25-27, and 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. ("54", PTO-1449 submitted November 7, 2001) and Barrett-Connor et al. ("4", PTO-1449 submitted November 7, 2001), and Do Nascimento (of record) in view of Labrie et al. (WO 96/26201, PTO-1449 submitted November 7, 2001), for the same reasons of record in the Office Action dated August 13, 2003.

Luo et al. discloses that an estrogen, DHEA alone, or the particular SERM (antiestrogen), EM-800 alone (having 2S configuration and moieties convertible in vivo to hydroxyl), is known to be useful in a method of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels. See abstract and page 4436 Fig. 1 "Structure of EM-800", page 4438 the left column "Effect on serum lipid levels". Luo et al. further discloses that the combination of DHEA and EM-800 exerts

more potent effect on reducing serum lipid levels than each compound used alone (page 4438 the left column "Effect on serum lipid levels" and page 4439 Fig. 4, and page 4443 the left column.

Barrett-Connor et al. teaches that SERMs are capable of lowering serum lipid levels to reduce the risk of coronary heart disease, as estrogen does. See abstract.

Do Nascimento teaches that the particular estrogen, 17β-estradiol, is useful in treating hypercholesterolemic patients (see abstract).

The prior art does not expressly disclose the employment of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or further combining with DHEA in a pharmaceutical composition.

Labrie et al. (WO 96/26201) discloses that both EM-800 and EM-652 are antiestrogens (SERMs), and EM-800 has moieties convertible in vivo to hydroxyl to become EM-652. Thus, EM-800 is a metabolite of EM-652, having the same functional property and activity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or to further combine with DHEA, in a pharmaceutical composition.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or to further combine with DHEA, in a pharmaceutical composition, since estrogens such as 17β-estradiol and DHEA are well

known in the art to be used in methods of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels according to the cited prior art herein. Moreover, the particular SERM, EM-800, a known metabolite of EM-652 (convertible in vivo to hydroxyl to become EM-652), alone or in combination with an estrogen such as DHEA, is known to be useful in a method of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels according to Luo et al.

Therefore, one of ordinary skill in the art would have reasonably expected that combining an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or further combining with DHEA, all known useful for the same purpose, i.e., treating hypercholesterolemia, would improve the therapeutic effects for treating the same disorder, hypercholesterolemia, and/or would produce additive therapeutic effects in treating the same. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) regarding combination inventions. It is considered prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose.

Further, the teachings of Luo et al. that the combination of DHEA and EM-800 exerts more potent effect on reducing serum lipid levels than each compound used alone clearly provides the motivation of the instant claimed method employing the combination of EM-652, 17β-estradiol and DHEA.

Furthermore, one of ordinary skill in the art would have been motivated to prepare a kit comprising the same composition because the preparation of a kin

comprising a pharmaceutical composition is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Response to Argument

Applicant's arguments filed February 17, 2004 with respect to the rejection of claims 9-16 made under 35 U.S.C. 103(a) as being unpatentable over Ofner et al. (EP 0707006 A1) in view of Russell et al. and Clauw et al. record in the previous Office Action July 15, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant asserts that the obviousness rejection is based, in part, on a misunderstanding of the teaching of Luo since DHEA is not an estrogen. However, the rejection is primarily based on the teachings of Luo et al. that the combination of DHEA and EM-800 exerts more potent effect on reducing serum lipid levels than each compound used alone (page 4438 the left column "Effect on serum lipid levels" and page 4439 Fig. 4, and page 4443 the left column.

Applicant also asserts that "Applicant has surprisingly found that SERMs and estrogens can provide significant benefits when used in combination", but absent any supporting data for this assertion as further discussed. Note that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang,

100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

More importantly, it has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. In the instant case, as discussed in the 103(a) rejection in the previous Office Action, EM-800 alone (having 2S configuration and moieties convertible in vivo to hydroxyl), is known to be useful in a method of treating hyperlipidemia by decreasing serum lipid levels such as triglyceride and cholesterol levels according to Luo et al. Moreover, SERMs in general are known to be capable of lowering serum lipid levels to reduce the risk of coronary heart disease, as estrogen does based on the teachings of Barrett-Connor et al. Estrogens such as 17β-estradiol, are also known to lower serum cholesterol. Therefore, one of ordinary skill in the art would have reasonably expected that combining the particular SERM, EM-652.HCl, and the particular estrogen, 17β-estradiol, known useful for the same purpose, i.e., lowering serum lipid levels in a composition to be administered would improve the therapeutic effect for treating hyperlipidemia, absent evidence to the contrary.

Therefore, motivation to combine the teachings of the prior art to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Further, Applicant's testing results in Examples of the specification have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed combination but are not deemed persuasive for the following reasons. The results herein are not seen to provide clear and convincing evidence of nonobviousness or unexpected results over the cited prior art for the combination of 17β-estradiol and the particular SERM, EM-652.HCl, or further combining with DHEA in the claimed method of hyperlipidemia. The specification provides no side-by-side comparison with the closest prior art.

Moreover, the evidence in the testing is not commensurate in scope with the claimed invention and does not demonstrate criticality of the claimed range of active agents herein in the claimed method.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a).

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

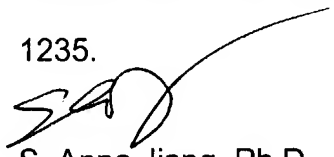
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.



S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
April 28, 2004